Safety analysis of proposed pegfilgrastim biosimilar in Phase I and Phase III studies

Nadia Harbeck¹, Jessie Wang², Gordon Philipp Otto³, Sreekanth Gattu³ & Andriy Krendyukov^{*,3}

¹Breast Center, Department of Obstetrics and Gynecology, University of Munich (LMU), Munich 81377, Germany

²Sandoz Inc., Princeton, NJ 08540, USA

³Hexal AG, Holzkirchen 83607, Germany

*Author for correspondence: Tel.: +49 8024 4764855; akrendyukov@gmx.de

Aim: This analysis compares safety data for Sandoz proposed biosimilar (LA-EP2006) and reference pegfilgrastim from a Phase I pharmacokinetic/pharmacodynamic study in healthy volunteers (HVs) and two Phase III confirmatory studies in patients with breast cancer (BC; total n = 808). **Patients & methods:** Baseline characteristics were summarized, and event rates of bone pain and headache calculated. **Results:** HVs in the Phase I pharmacokinetic/pharmacodynamic study were generally younger, with lower mean body mass index, versus BC patients in PROTECT-1/-2. Bone pain was the most frequent adverse event with similar incidences with reference versus proposed biosimilar in all studies. **Conclusion:** No differences in adverse events were found between Sandoz proposed biosimilar and reference pegfilgrastim, notwithstanding some differences between HVs and BC patients.

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Recombinant G-CSF therapies, such as filgrastim and the long-acting pegylated form (pegfilgrastim), are widely used to prevent neutropenic complications associated with myelosuppressive chemotherapy in oncological patients [1]. Neutropenia is correlated with risk of infection, and its associated mortality, in patients undergoing cytotoxic chemotherapy [2,3].

Febrile neutropenia (FN) is considered a medical emergency. It is associated with chemotherapy dose delays and reductions, and decreased relative dose intensity is linked to reduced survival [3,4]. In addition, FN often leads to prolonged hospitalization and has a considerable impact on patients' quality of life, as well as healthcare systems [2].

G-CSFs can be used as prophylaxis to reduce the risk of FN, supporting the delivery of myelosuppressive chemotherapy regimens at the planned dose [3,5], and as a consequence may lead to improved overall survival [6]. Primary prophylaxis with G-CSF has been shown to reduce the relative risks of FN, infection-related mortality and early deaths [7].

International evidence-based guidelines recommend G-CSF prophylaxis for patients receiving chemotherapy regimens with an FN risk of 20% or greater, and for those treated with chemotherapy regimens with an FN risk of between 10 and 20% if they also have risk factors such as previous FN and age ≥ 65 years [3,5,8].

No clinically meaningful differences in safety, efficacy or immunogenicity were reported between G-CSFs (filgrastim and pegfilgrastim) and their biosimilars in a recently published meta-analysis of randomized clinical trials carried out in patients with breast cancer (BC) [9]. Biosimilars are approved biologics in highly regulated markets that have been proven to match attributes of the reference medicine, including clinical safety, efficacy and immunogenicity, with no meaningful differences in clinical performance [10]. Filgrastim biosimilars, based on the reference biologic Neupogen[®] (Amgen), have been licensed in Europe for over 10 years and, in 2015, Sandoz biosimilar filgrastim (Zarxio[®]) was the first biosimilar medicine approved by the US FDA [11].

Pegfilgrastim biosimilars are currently under development, with some having recently been approved by the FDA and the European Medicines Agency. Pegylation of filgrastim leads to reduced renal clearance and therefore

once-per-chemotherapy cycle administration [12]. It has been previously reported that pegfilgrastim and filgrastim display comparable efficacy and safety, however, pegfilgrastim's once-per-cycle administration [13,14] may offer cancer patients undergoing myelosuppressive chemotherapy more convenience, potentially resulting in improved patient compliance and clinical outcomes [15–17].

A proposed biosimilar pegfilgrastim (LA-EP2006) has been developed by Sandoz. State-of-the-art analytical procedures have demonstrated that Sandoz proposed biosimilar pegfilgrastim matches the reference medicine (Neulasta®, Amgen) in terms of primary and higher order structure, biological activities, functional characterization and other physicochemical properties. Furthermore, two confirmatory, randomized, double-blind, Phase III studies in patients with BC (PROTECT-1 and PROTECT-2) reported no clinically meaningful differences in efficacy, safety and immunogenicity between Sandoz proposed biosimilar pegfilgrastim and the reference medicine [18–20].

Bone pain is the most common and consistently observed adverse event (AE) reported across clinical trials of different types of recombinant human G-CSF (lenograstim, filgrastim, pegfilgrastim and their biosimilars) in both healthy volunteers (HVs) and patients with cancer [9,21,22]. Bone pain is associated with the direct and indirect actions of G-CSF, mainly on bone remodeling osteoblasts and osteoclasts, and partially on immune cells and neurons. This involves quantitative and qualitative expansion of bone marrow, peripheral nociceptor sensitization to nociceptive stimuli, modulation of immune function and direct effect on bone metabolism [22]. With reference pegfilgrastim, bone pain has been reported at incidences of 25–38% among oncological patients and 52–84% among healthy donors for allogeneic transplantation [22].

Confirmatory clinical data supporting the totality-of-evidence as well as studies in a sensitive population are required for biosimilar development. This safety analysis pooling data from HVs and patients with BC to provide a large population was performed to further investigate the safety profile of proposed biosimilar pegfilgrastim. Safety data for Sandoz proposed biosimilar pegfilgrastim and reference pegfilgrastim was compared in HVs and in patients with cancer, using data from the registration Phase I pharmacokinetic (PK)/pharmacodynamic (PD) study and the Phase III confirmatory studies, PROTECT-1 and PROTECT-2.

Methods

Aim

The aim of this analysis is to compare safety data for Sandoz proposed biosimilar pegfilgrastim across three randomized controlled trials (RCTs); the first being a single-dose, randomized, double-blind, crossover, Phase I PK/PD study in HVs receiving proposed biosimilar or reference pegfilgrastim (Neulasta®; EudraCT number 2015-003752-51) [23]. The other studies were two randomized, double-blind, Phase III confirmatory trials PROTECT-1 (EudraCT number 2011-004532-58; NCT01735175) [18,19] and PROTECT-2 (EudraCT number 2012-002039-28; NCT01516736) [19,20] in patients with BC undergoing cytotoxic chemotherapy and concomitant treatment with proposed biosimilar pegfilgrastim or the reference biologic (Neulasta®).

The frequency of AEs for a single dose of pegfilgrastim in the Phase I PK/PD study were compared with AEs associated with the first treatment cycle of docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (TAC regimen), plus pegfilgrastim in PROTECT-1 and -2.

Study designs & populations

The Phase I PK/PD study was a single-dose, randomized, double-blind, crossover study in HVs conducted between February 2016 and January 2017 [23]. In this crossover study, 92 HVs were administered a single 6 mg subcutaneous dose of Sandoz proposed biosimilar pegfilgrastim and 92 HVs were administered a single 6 mg subcutaneous dose of reference pegfilgrastim.

PROTECT-1 was a randomized, double-blind, Phase III confirmatory study in 316 patients with BC undergoing cytotoxic chemotherapy (≤6 cycles) and receiving Sandoz proposed biosimilar (n = 159) or reference pegfilgrastim (n = 157), conducted between June 2012 and February 2014 at 42 study sites in six countries [18].

PROTECT-2 was also a randomized, double-blind, Phase III confirmatory study in 308 patients with BC undergoing cytotoxic chemotherapy (≤6 cycles) and receiving Sandoz proposed biosimilar (n = 155) or reference pegfilgrastim (n = 153), conducted between March 2012 and December 2013 at 53 study sites in eight countries [20].

Statistical analysis

Baseline characteristics were summarized, and mean and standard deviation (SD) were provided for age, gender and body mass index (BMI). Frequency analyses were conducted to calculate the event rate of bone pain and headache

Table 1. Baseline characteristics of the study populations of the Phase I pharmacokinetic/pharmacodynamic study, PROTECT-1 and PROTECT-2.

Group	Phase I PK/PD study		PROTECT-1		PROTECT-2	
	Sandoz proposed biosimilar pegfilgrastim/reference pegfilgrastim n = 176	Reference pegfilgrastim/Sandoz proposed biosimilar pegfilgrastim n = 178	Sandoz proposed biosimilar pegfilgrastim n = 159	Reference pegfilgrastim n = 157	Sandoz proposed biosimilar pegfilgrastim n = 155	Reference pegfilgrastim n = 153
Age (years), mean (SD)	26.3 (6.80)	27.1 (7.90)	49.9 (9.53)	50.5 (10.87)	48.8 (10.50)	49.1 (10.07)
Female sex, n (%)	34 (37)	33 (36)	159 (100)	157 (100)	155 (100)	153 (100)
BMI (kg/m ²), mean (SD)	24.2 (2.30)	23.5 (2.00)	27.5 (26.76)	27.4 (26.35)	26.6 (5.77)	26.5 (5.13)

BMI: Body mass index; n: Number of patients/healthy volunteers in treatment group; PD: Pharmacodynamic; PK: Pharmacokinetic; SD: Standard deviation.
Phase I PK/PD study results adapted from Nakov *et al.* 2018 [23]; PROTECT-1 study results adapted from Harbeck *et al.* 2016 [18]; and PROTECT-2 study results adapted from Blackwell *et al.* 2016 [20].

by treatment. Relative risks and 95% confidence intervals (CIs) were calculated based on the event rates for bone pain and headache for treatment comparison, respectively. The analyses used PROC FREQ procedure in SAS[®] version 9.4.

Results

Baseline characteristics

The baseline characteristics of the three study populations are described in Table 1. The combined safety analysis populations in the Phase I PK/PD study, PROTECT-1 and PROTECT-2 include 92 HVs and 314 patients with BC that received Sandoz proposed biosimilar pegfilgrastim, and 92 HVs and 310 patients with BC that received the reference biologic (Table 1) [18,20,23].

The HVs in the Phase I PK/PD study were generally younger (mean age was approximately 27 years) compared with the patients in PROTECT-1 and -2 (mean age was approximately 50 years and 49 years, respectively) (Table 1) [18,20,23].

In the Phase I PK/PD study, 64% of participants were male, while only female patients were included in the PROTECT-1 and -2 studies (Table 1). Mean BMI was lower in the Phase I PK/PD participants (23.9 kg/m²) compared with PROTECT-1 (approximately 27.5 kg/m²) and PROTECT-2 (approximately 26.5 kg/m²) (Table 1) [18,20,23].

Bioequivalence & clinical efficacy

In the Phase I PK/PD study, bioequivalence was demonstrated between Sandoz proposed biosimilar pegfilgrastim and the reference medicine as the 90% CIs for the geometric mean ratio of the PK parameters, and the 95% CIs for the PD parameters, were completely contained within the prespecified range of 0.8–1.25 [22].

Sandoz proposed biosimilar pegfilgrastim matched the reference medicine in terms of efficacy in both the PROTECT-1 and -2 studies [18,20]. Similar mean duration of severe neutropenia was reported for proposed biosimilar and reference pegfilgrastim in the two studies, with the 90 and 95% CIs for treatment difference being within the predefined equivalence margin of 1 day [18,20]. Moreover, no significant differences in secondary efficacy end points (including mean depth of absolute neutrophil count nadir, mean time to absolute neutrophil count recovery, number of episodes of FN, number of infections and mortality from infection) were reported in either study [18,20].

Treatment-related AEs

In the Phase I PK/PD study in HVs, Sandoz proposed biosimilar pegfilgrastim matched the reference medicine in terms of safety profile [23]. With proposed biosimilar and reference pegfilgrastim, treatment-emergent adverse events (TEAEs) related to the study drug occurred in 95 and 96% of subjects, respectively. The most commonly reported drug-related TEAEs following Sandoz proposed biosimilar pegfilgrastim and reference pegfilgrastim administration, respectively, were headache (57.0 and 56.0%), bone pain (58.0 and 53.0%), myalgia (36.0 and 45.0%) and back pain (30.0 and 25.0%). TEAEs were generally mild and no serious AEs were reported in the Phase I PK/PD study.

Table 2. Bone pain and headache in healthy volunteers and patients with breast cancer treated with proposed biosimilar or reference pegfilgrastim.

Adverse event	Proposed biosimilar, n (%)	Reference, n (%)
Bone pain		
Phase I PK/PD study	102 (58)	94 (53)
PROTECT-1	7 (4.4)	6 (3.8)
PROTECT-2	7 (4.5)	13 (8.5)
Headache		
Phase I PK/PD study	100 (57)	99 (56)
PROTECT-1	2 (1.3)	3 (1.9)
PROTECT-2	3 (1.9)	3 (2.0)

n: Number of patients/healthy volunteers with the adverse event; PD: Pharmacodynamic; PK: Pharmacokinetic.

Phase I PK/PD study results adapted from Nakov *et al.* 2018 [23]; PROTECT-1 study results adapted from Harbeck *et al.* 2016 [18]; and PROTECT-2 study results adapted from Blackwell *et al.* 2016 [20].

The safety profile of Sandoz proposed biosimilar pegfilgrastim also matched that of the reference in the two PROTECT trials [18,20]. In PROTECT-1, 88.1 and 82.8% of patients receiving proposed biosimilar and reference pegfilgrastim experienced one or more TEAEs, respectively, with alopecia (51.6 and 50.3%), nausea (40.9 and 37.6%), asthenia (39.6 and 35.7%), vomiting (21.4 and 21.7%) and neutropenia (17.0 and 21.7%) reported as the most common [18]. TEAEs related to the study drug occurred in 11.9% of patients who received Sandoz proposed biosimilar pegfilgrastim and 14.6% of patients who received the reference medicine. Treatment-related bone pain was reported by 4.4% of patients receiving biosimilar pegfilgrastim and 3.8% of patients receiving the reference medicine. In total, six deaths (four in the proposed biosimilar and two in the reference pegfilgrastim groups) were reported during the study, none were related to pegfilgrastim.

Overall, 96.1% of patients receiving Sandoz proposed biosimilar pegfilgrastim and 95.4% of patients receiving the reference medicine experienced TEAEs in the PROTECT-2 trial [20]. Over all cycles, the incidence of TEAEs considered related to study treatment was 33.5 and 28.1% with proposed biosimilar and reference pegfilgrastim, respectively. Treatment-related bone pain was reported by 4.5% of patients receiving Sandoz proposed biosimilar pegfilgrastim and 8.5% of patients receiving the reference medicine. Serious TEAEs related to study treatment occurred in 2.6% of patients who received proposed biosimilar pegfilgrastim and 0.7% of patients who received the reference medicine. Overall, five deaths (three in the proposed biosimilar and two in the reference pegfilgrastim groups) were reported during the study; again, none were related to pegfilgrastim. TEAEs were generally mild to moderate in PROTECT-1 and PROTECT-2 [18,20].

Frequencies of reported bone pain and headache in the Phase I PK/PD study, PROTECT-1 and PROTECT-2 are summarized in Table 2 and Figure 1.

Immunogenicity

In the Phase I PK/PD study, both Sandoz proposed biosimilar and reference pegfilgrastim had low incidences of anti-drug antibodies with no neutralizing or clinically relevant antibodies detected [23].

No neutralizing anti-drug antibodies against filgrastim, pegfilgrastim or polyethylene glycol were identified after dosing in any patient during the PROTECT-1 or -2 studies [18,20].

Discussion

Biosimilar development is based on the totality-of-evidence approach, in which a stepwise series of comparisons shows that a biosimilar matches its reference biologic. Clinical data from trials in a sensitive patient population are then considered confirmatory. Availability of safety data is important for clinicians to understand the safety profile of a proposed biosimilar medicine, and confirm that it matches that of the reference biologic. Clinical equivalence between Sandoz proposed biosimilar pegfilgrastim and the reference biologic has been demonstrated in two Phase III confirmatory, randomized clinical trials in patients with BC [18–20]. BC is considered a sensitive patient population for G-CSF biosimilar development, since G-CSF has a large effect on the relevant end point (by preventing neutropenic complications associated with myelosuppressive chemotherapy), and so differences between the biosimilar and the reference medicine are detectable [24]. Patients with BC receiving (neo)adjuvant therapy are a homogeneous patient population as they are chemotherapy naïve, and therefore will not have

Figure 1. Relative risk of bone pain and headache in healthy volunteers and patients with breast cancer treated with proposed biosimilar or reference pegfilgrastim.

Phase I PK/PD study results adapted from Nakov *et al.* 2018 [23]; PROTECT-1 study results adapted from Harbeck *et al.* 2016 [18]; and PROTECT-2 study results adapted from Blackwell *et al.* 2016 [20].

PD: Pharmacodynamic; PK: Pharmacokinetic.

experienced chemotherapy-induced immunosuppression, resulting in lower inter-patient variation concerning risk of treatment-related toxicity and higher sensitivity for assessing immunogenicity risk [24]. TAC chemotherapy (docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²) is an appropriate setting, as the effect of primary prophylaxis with G-CSF in patients receiving TAC is well documented in literature [25,26].

The Phase I PK/PD study confirmed bioequivalence of Sandoz proposed biosimilar pegfilgrastim to the reference medicine, and found no clinically meaningful differences in safety and immunogenicity between the two biologics in HVs [22]. This, combined with the results of the two Phase III confirmatory studies in patients with BC, support the matching safety and efficacy of Sandoz proposed biosimilar and reference pegfilgrastim [18,20,23]. AEs were reported at a similar frequency with Sandoz proposed biosimilar and reference pegfilgrastim in studies of patients with BC and HVs [18,20,23].

Bone pain was the most frequent AE in this combined safety analysis of the Phase I PK/PD study, PROTECT-1 and PROTECT-2. Bone pain related to pegfilgrastim treatment was reported at similar incidences in the reference group (53.0, 3.8 and 8.5%, respectively) compared with the proposed biosimilar group (58.0, 4.4 and 4.5%, respectively) in the three studies [18,20,23]. Although AEs, including bone pain, were reported at similar rates in the proposed biosimilar and reference pegfilgrastim groups, AEs were generally reported at a higher frequency in the Phase I PK/PD study compared with the Phase III confirmatory PROTECT-1 and -2 studies.

Bone pain is a known side effect for G-CSF therapies, and has previously been reported in 25–42% of patients enrolled in randomized, double-blind studies [22,27–32]. Reported frequencies of G-CSF-induced bone pain varies between controlled clinical trials and large, prospective, observational studies: musculoskeletal or bone pain was reported in 5.6% of patients in the HEXAFIL study [33], compared with 24.7% of patients reporting bone pain in the MONITOR-GCSF study (Table 3) [34]. This may reflect differences in patient populations, use of concomitant medications and how bone pain was assessed [35,36].

Baseline health status is a major difference between the three study populations. Phase I PK/PD study participants were apparently healthy, whereas PROTECT-1 and -2 study participants had a confirmed diagnosis of stage I to IV BC and were also administered concomitant TAC chemotherapy as part of their BC treatment regimes. The differences in AEs reported in the Phase I PK/PD study and PROTECT-1 and -2 are most likely due to differences in the study populations, use of concomitant medication, baseline health status (healthy vs BC) and concomitant TAC chemotherapy administered to the patients with BC participating in PROTECT-1 and PROTECT-2.

Table 3. Incidence of bone pain and headache in the Phase I pharmacokinetic/pharmacodynamic study, PROTECT-1, PROTECT-2 and the two observational studies HEXAFIL and MONITOR-GCSF.

TEAE	Phase I PK/PD study		PROTECT-1		PROTECT-2		HEXAFIL	MONITOR-GCSF
	Sandoz proposed biosimilar pegfilgrastim N = 176	Reference pegfilgrastim N = 178	Sandoz proposed biosimilar pegfilgrastim N = 159	Reference pegfilgrastim N = 157	Sandoz proposed biosimilar pegfilgrastim N = 155	Reference pegfilgrastim N = 153	Sandoz proposed biosimilar filgrastim N = 1473	Sandoz proposed biosimilar filgrastim N = 1496
Bone pain TEAE, n (%)	102 (58.0)	94 (53.0)	7 (4.4)	8 (5.1)	10 (6.5)	17 (11.1)		357 (24.7)
Bone pain TEAE related to pegfilgrastim, n (%)	102 (58.0)	94 (53.0)	7 (4.4)	6 (3.8)	7 (4.5)	13 (8.5)	48 (3.3) [†]	NR (23.0)
Headache TEAE, n (%)	101 (57.0)	100 (56.0)	5 (3.1)	9 (5.7)	21 (13.5)	13 (8.5)		100 (6.9)
Headache TEAE related to pegfilgrastim, n (%)	100 (57.0)	99 (56.0)	2 (1.3)	3 (1.9)	3 (1.9)	3 (2.0)	3 (0.2) ^{†,‡}	

[†] Possible relationship to filgrastim in all patients.

[‡] Reported as 'Neurology'.

N: Number of patients/healthy volunteers in cohort; n: Number of patients/healthy volunteers with the adverse event; NR: Not reported; PD: Pharmacodynamic; PK: Pharmacokinetic; TEAE: Treatment-emergent adverse event.

Phase I PK/PD study results adapted from Nakov *et al.* 2018 [23]; PROTECT-1 study results adapted from Harbeck *et al.* 2016 [18]; PROTECT-2 study results adapted from Blackwell *et al.* 2016 [20]; HEXAFIL study results adapted from Tesch *et al.* 2015 [33]; MONITOR-GCSF study results adapted from Gascon *et al.* 2016 [34].

The Phase I PK/PD study participants were younger (approximate mean age was 27 vs 50 and 49 years), of both male and female sex (36% female vs 100% female) and leaner (mean BMI was 23.9 kg/m² vs approximately 27.5 kg/m² and 26.6 kg/m²) than PROTECT-1 and -2 study participants, which all may influence perception of pain (bone pain and headache) [37,38]. It should also be noted that since the Phase I PK/PD study participants were healthy, it could be assumed that no pain is present at baseline. Indeed, this study employed a 0–100 mm visual analog scale to assess local tolerance at the injection site and scores indicated that the majority of HVs had no pain at baseline [23]. At 1-hour post-dose, the mean (SD) visual analog scale scores were 0.5 (2.03) and 1.2 (3.75) following Sandoz proposed biosimilar and reference pegfilgrastim administration, respectively [23]. Perception and experience of pain is more likely in patients with BC due to disease progression and side effects of other medications [39]. Therefore, patients with BC might not recognize G-CSF-induced pain to the same extent as HVs. Furthermore, the difference between incidence of pain in HVs and in patients with BC may reflect the differences reported in RCTs and real-world evidence, suggesting variation in perception of pain in different clinical settings.

Sex differences have been identified in the reporting of AEs [40], and it is possible that the 64 versus 0% proportions of males in the Phase I PK/PD study, compared with PROTECT-1 and -2, may influence the perception and reporting of patient-reported AEs such as bone pain and headache in the different studies. For example, in a safety analysis of 4870 patients (46% females, 54% males) reporting 264 AEs (59.1% in males), females compared with males had a statistically higher incidence of drug-related pain AEs (37.6 vs 20.8%; *p* = 0.0039), and more AEs in female patients were addressed with treatment compared with AEs in male patients (78.1 vs 66.7%; *p* = 0.0485) [41]. However, this trend for a higher incidence of pain AEs in women contrasts with the lower incidence of bone pain and headache seen in the all-female populations in the PROTECT studies compared with the Phase I PK/PD study.

Comparisons of AEs across clinical trials have limitations due to differences in reporting of musculoskeletal/bone pain, recording of AEs, patient populations, chemotherapy regimens and clinical settings [20,42]. Within the studies, there were no differences in incidence of bone pain or headache between Sandoz proposed biosimilar pegfilgrastim and the reference medicine, in both HVs (mixed population), as well as in patients with BC (female population) [18,20,23].

Conclusion

In summary, no differences in AEs, including bone pain and headache, were observed between Sandoz proposed biosimilar and reference pegfilgrastim in three RCTs, including two Phase III confirmatory studies in patients with

BC receiving myelosuppressive chemotherapy. These findings support the matching clinical safety and efficacy of Sandoz proposed biosimilar pegfilgrastim and the reference biologic.

Future perspective

The global burden of cancer is rising, with >18 million new cases and >9.5 million deaths reported worldwide in 2018 [43], and 21 million new cases and 13 million deaths expected annually by 2030 [44]. Although the number of new cases is increasing, survival in some early cancers has improved due to factors including advances in diagnosis and the introduction of biologic medicines. Biologics have transformed the care of many oncology patients, however their high cost presents challenges to healthcare systems [45].

Biosimilars such as G-CSF and erythropoiesis-stimulating agents have been used in supportive care in oncology for over a decade. Monoclonal antibody biosimilars used in curative or advanced disease settings in oncology are becoming increasingly available, and include biosimilars of trastuzumab, bevacizumab and rituximab [46–58]. Biosimilars in oncology offer the opportunity for cost savings, increased access to biologic agents and reinvestment of funds for new drug development. However, the potential of biosimilars to progress cancer treatment and improve clinical outcomes is dependent on their acceptance. This may be aided by the availability and publication of data for biosimilars in oncology, including safety data from both RCTs and from real-world evidence. Such data can help instil confidence in clinicians regarding use of biosimilars. Other steps to improve the acceptance of biosimilars should include guidance from regulatory bodies, and education for both clinicians and patients to enhance understanding and address misconceptions regarding biosimilars [6,59]. Only once the challenge of acceptance is overcome can the full potential of biosimilars be realized.

Executive summary

Background

- Bone pain is one of the most common adverse events (AEs) reported with G-CSF and their biosimilars.

Results

- Bone pain was the most frequently reported AE in both healthy volunteers and in patients with breast cancer.
- Bone pain related to study treatment was reported at similar incidences in the reference group versus the proposed biosimilar group in three studies.

Discussion

- No differences in AEs, including bone pain and headache, were found between Sandoz proposed biosimilar and reference pegfilgrastim, notwithstanding some differences between healthy volunteers and breast cancer patients.
- Results from these three randomized controlled studies support the matching clinical safety and efficacy of Sandoz proposed biosimilar pegfilgrastim and the reference biologic.

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Authors' contributions

N Harbeck participated in the design of the study, the writing of the paper and approved the final version of the paper for submission. J Wang participated in the design of the study, the statistical analysis of the study, the writing of the paper and approved the final version of the paper for submission. G Otto participated in the design of the study, the writing of the paper and approved the final version of the paper for submission. S Gattu participated in the design of the study, the writing of the paper and approved the final version of the paper for submission. A Krendyukov participated in the design of the study, the writing of the paper and approved the final version of the paper for submission. All authors agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: EudraCT number 2015-003752-51; EudraCT number 2011-004532-58 (NCT01735175); EudraCT number 2012-002039-28 (NCT01516736).

Data deposition

Data from previously published reports were used in this analysis and can be found online using the PubMed/Medline database: Nakov *et al.* 2018 www.ncbi.nlm.nih.gov/pubmed/30079636 [PMID: 30079636]; Harbeck *et al.* 2016 www.ncbi.nlm.nih.gov/pubmed/27020170 [PMID: 27020170]; Blackwell *et al.* 2016 www.ncbi.nlm.nih.gov/pubmed/27091420 [PMID: 27091420].

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